SPECTRUM OF NEPHROTIC SYNDROME IN ADULTS IN BUNDELKHAND REGION
A CLINICO-PATHOLOGICAL STUDY

THESIS

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C E R T I F I C A T E

This is to certify that the work entitled "SPECTRUM OF NEPHROTIC SYNDROME IN ADULTS IN BUNDELKHAND REGION : A CLINICOPATHOLOGICAL STUDY", which is being submitted as a thesis for M.D.(Medicine) Examination, 1992 of Bundelkhand University by RAKESH KUMAR SHARMA , has been carried out in the department of Medicine, M.L.B. Medical College, Jhansi.

He has put in the necessary stay in the department of Medicine as per university regulations.

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A C K N O W L E D G E M E N T S

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Dated:

R. K. Sharma

(Rakesh Kumar Sharma)

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I N T R O D U C T I O N

I N T R O D U C T I O N

Nephrotic syndrome is a common end point of variety of disease processes damaging the permeability properties of glomerular capillary wall. Heavy proteinurea is the hallmark of the nephrotic state. Arbitrarily protein excretion rate in excess of 3.5 gm/1,73 m^2 of body surface area/day is considered to be in nephrotic range.

This massive proteinurea may result into hypoalbuminemia, oedema and hyperlipidaemia.

Spectrum of nephrotic syndromes varies in different ethnic population, age groups and socio-economic strata. Tropical countries have been shown to have piculiar distribution of this illness but there are regional differences as well.

The exact incidence of this condition is difficult to assess due to its low prevalence. The chronicity and refractory nature of it to treatment prevents a long follow up making it difficult to predict the prognosis. Though it is generally agreed that minimal lesion group predominates in children and other varieties of glomerulonephritis are common presentation in the adult group.

Nephrotic syndrome results not merely from several intrinsic renal diseases but also from a number of systemic diseases secondarily involving the kidneys.

Introduction of percutaneous renal biopsy by Iverson and Brun has helped us to understand the pathogenesis and improve our therapeutic and prognostic approach to nephrotic syndrome.

There have been detailed studies correlating the histology and the clinical presentation with biochemical freatures of the individual lesions. Generally the correlation is of benefit, in predicting the response to therapy and prognosis.

Various studies conducted in our country have revealed interesting variations in the etiology of nephrotic syndrome.

In India tuberculosis is a serious health problem. The prevalence of infection of tuberculosis is about 30% and prevalence of disease is about 4 per 1000 population.

In Bundelkhand region, tuberculosis is even more prevalent than other parts of India and it is frequently found to be associated with nephrotic syndrome.

A I M S A N D O B J E C T I V E S

AIMS AND OBJECTIVES

The present study was conducted with the following aims and objectives.

- To study the etiopathogenesis of nephrotic syndrome with special reference to pulmonary tuberculosis and the clinical spectrum of the nephrotic syndrome in Bundelkhand region of Uttar Pradesh.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Domenico Cotugno described a young shoulder whose urine coagulated like soft white of an egg, when heated and he had massive oedema.

Richard bright (1836) was the first physician to demonstrate that the excretion of albuminous urine was a mark of serious renal disease. Bright demonstrated that albuminous urine was an important sign which preceeds any clinical feature of structural alteration of kidney.

Renal biopsies indicated that proteinurea is a sign of structural change in the kidney (Iversen and Brum, 1951). Definite histopathological changes were found out associated with proteinurea with the half of height and electron microscope.

Walker et al (1942) measured glomerular filterate of animals by using nephron puncture technique. They proved that glomerulus was relatively impermeable to the passage of albumin and glomerular filterate contained very little amount of albumin.

On the molecular level Farquhar and Palade(1961) pioneered the use of combining tracer proteins with the aminonucleoside model to follow passage of proteins through the glomerulus. Further improvement in this area was done by Venkatachalam Karnovaky and Cotran (1969). Tamm and Horsfall (1952) isolated and characterised proteins produced by kidneys. They also discovered urokinase and

secretory IgA. Excretion of low molecular weight proteins in certain diseases has focussed attention on the kidney as a homeostatic mechanism for reclaiming proteins but it is not due to break down of glomerular barrier but rather to impairment of reabsorptive process or catabolic process.

The type of protein excreted in renal disease depends upon the specific nature of the disease. Protein excretion pattern associated with renal tubular disease was different from that found in glomerular disease (Butler and Flaynn, 1958).

MECHANISM OF PROTEIN EXCRETION

Tubular Proteinurea

Normal, low molecular weight (<40,000) serum proteins such as beta-2 microglobulins (11,600 mol. wt.), Lysozyme (14,000 mol. wt.) or light chain (22,000 molt wt.) are readily filtered by glomeruli but are reabsorbed so efficiently that only trace amount enters the urine. Diseases that selectively damage tubules more than glomeruli, cause excessive excretion of these small proteins with little or no increase in albumin excretion. The resulting proteinurea is usually between 1-3 gm/24 hours and oedema and lipid disorders do not occur because albumin disorders are small. Bene Jones proteins which is probably a dimer of two light chains. Light chains themselves, and myoglobins are example of proteins whose plasma concentration may increase as a consequence of

of disease. If their filtered load rises enough to exceed tubular reabsorptive capacity, overflow proteinurea may occur.

Glomerular proteinurea

Normal glomeruli filter very little albumin or globulin. Glomerular capillary endothelium form a barrier penetrated by pores of about 1000 A° diameter that holds back cells and other particles but offers no impediment to most proteins. The glomerular basement membrane traps molecules about 50 A° in effective radius above 100,000 daltons molecular mass. The foot processes (Podocytes) of visceral epithelial cells cover the urinary aspect of glomerular basement membrane and it produces a series of narrow channels through which molecules that travers the basement membrane must pass.

Anionic molecules, like albumin are filtered less freely than neutral or positively charged molecules of the same size so very little albumin enters the filterate. Thus charge selectively appears to be due to anionic glycoproteins that cover the surface of foot processes and contributes to matrix structure of basement membrane. The glycoproteins are anionic because they contain the dicarboxylic amino acids e.g. glutamic, aspartic acid and sealic acid. At the pH of blood (7.4) of urine (4.5 to 7.5) carboxylic and zialic acid residues are dissociated and therefore have a negative change. Albumin also carries

an overall negative charge. The negatively charged of glycoproteins repel those of albumin and retard filtration. Glomerular disease can disrupt any of these filteration barriers. Injury limited to polyionic glycoproteins would tend to produce selective losses of anionic proteins, such as albumin. Extensive injury that involves the entire basement membrane, not only its polyionic compartment, may increase losses of very large proteins as well as albumin.

Quantity of Proteinurea

Protein excretion is abnormal when the total daily excretion exceeds 150 mg (Reiman and Levinsky, 1971). For any given rate of protein excretion the concentration of protein in a single voided urine sample will vary inversely with the urine flow. However, even at low flow rates the concentration of protein in normal urine does not exceed 10-20 mg/dl. Thus the occurrence of a higher concentration in any specimen of urine implies the existence of proteinurea. Protein excretion above 3.5 gm/24 hour is termed massive proteinurea and usually occurs when glomeruli have been damaged enough to allow plasma proteins, especially albumin to enter the urine.

The kidneys from patients with nephrotic syndrome usually do not show the inflammatory changes on glomerular lesions typical of nephritis. The presence of rate in the renal tubular cells and in casts

in the urine sediment suggested to early pathologists, that the major pathologic changes of this disorder were in renal tubules. To emphasize this finding Muller (1905) called this condition nephrosis. Researchers however, soon demonstrated that proteins found in the urine of patients with nephrotic syndrome consisting chiefly of albumin were identical to those circulating in the blood and were not of renal tubular origin. Walker (1941) proved that the origin of proteinurea and the prime site of the pathology of nephrotic syndrome lie in the glomerulus.

In some patients it was seen (Berman, 1958) that some patients had only gross proteinurea and lipidurea without oedema, hypercholesterolemia, hypoproteinuria and have been shown on biopsy to have the same kinds of pathologic changes that accompany the more classic syndromes.

In recent years the massive proteinurea alone became to represent the syndrome because massive protein loss connotes serious renal disease whether or not the losses are so disproportionate to nutritional state and hepatic albumin synthesis that hypoproteinemia has developed and oedema and lipid disturbances appeared.

Therefore the useful exact definition of nephrotic syndrome is massive urinary protein excretion (more than 3.5 gm/24 hour/1.73 m^2), the proteins being mainly albumin or generally reflecting the composition of serum proteins.

The other features such as elevated serum cholesterol, lowered serum albumin and oedema were not found in all the cases of nephrotic syndrome, therefore they were described as the variable (although common) findings of nephrotic syndrome (Berman, 1958).

Hypoproteinemia

Albumin is the major protein loss in the urine accounting for approximately 70% of the total(Kark,1958). Therefore, hypoalbuminemia accounts for most of the reduction in the protein concentration in the plasma. Though a degree of hypoglobulinemia may occur.

Even though the hypoalbuminaemia is not a constant finding of the nephrotic syndrome. In one series Schreiner found that hypoalbuminaemia was not present initially in 16 percent of cases. The variable tendency of hypoalbuminaemia was possibly dependent upon the amount and duration of the protein loss.

The loss of proteins in the urine is recognized as one aspect of the over all turn over the plasma proteins, as they are continually being metabolised and constantly replaced by newly synthesized protein molecules. The normal amount of protein catabolised and that excreted in urine is off set by synthesis. Catabolism and synthesis are both quite dynamic, for in man it has been shown that about one tenth of the plasma mass of the protein is broken down each day.

The albumin is synthesized in liver at about 8-14 gm/day for a 70 kg person. It is balanced by normal rates of albumin degradation and it is capable of increasing somewhat in response to increased demand. An important normal control stimulus for albumin production is the oncotic pressure of plasma protein.

Some nephrotic patients seem capable of remaning in albumin balance (with low serum concentration) despite of massive proteinurea. Other are severely hypoproteinaemic even with lesser proteinurea. The poor appetite ill advised dietary protein restriction or malabsorption from edematous bowel may account for some limitation of albumin synthesis, but it appears likely that some other unknown impairment of liver function may be present as well in some nephrotic patients.

Jensen et al (1967), Waldman et al (1972) studied the disturbances in albumin metabolism in nephrotic patients and animals by using the radio-labelled albumin and found that endogenous fractional catabolic rate of albumin was increased in nephrotic patients. A likely explanation for this is increased exposure of albumin to renal tubular catabolic sites.

Katz et al (1963) found that the fractional catabolic rate of albumin of experimentally nephrotic rats was raised, however if a nephrectomy was performed this elevated catabolic rate dropped to a large extent, indicated that the increased catabolism occurred in the

kidney. Therefore in summary it would appear that hypoalbuminaemia is due primarily to the losses in the kidney and that this is augmented by an increased endogenous catabolism by the renal tubules.

OEDEMA

Oedema was the commonest presentation of most of the studies conducted in India and abroad.

The oedema represents the accumulation of visible or palpable excess quantities of interstitial fluid. For the oedema to be generalised, several litres of excess fluid must be present. In order for oedema formation to occur, fluid must move from the plasma across the capillary walls into the interstitial space and the kidneys must retain sufficient quantities of salt and water to account for the body's increased content.

The starling forces (oncotic pressure and hydrostatic pressure) determine the distribution of fluid between capillary and interstitial spaces. The oncotic pressure of plasma helps to retain the fluid inside the capillary. In nephrotic syndrome the oncotic pressure of plasma is decreased due to hypoalbuminemia which helps in the formation of oedema.

Squaire (1957) in his large series of cases has found reasonable correlation between occurrence and severity of oedema and degree of hypoproteinaemia, especially albumin concentration. Anasarca and oedema of limbs were found to occur when serum albumin levels

were below 1.6 g% and 1.8 g% respectively and never above the concentration of 3.9 g%.

But there was the lack of definite correlation between occurrence of generalised oedema and serum albumin concentration in some cases studied by Berman et al (1958), Mukerjee(1973) and Shanbhag et al(1973).

Shanbhag found a number of patients even at an albumin concentration of 1.1to1.2 g% without any oedema.

This lack of definite correlation between occurrence of generalised oedema and serum albumin concentration was explained by Berman on the basis that apart from albumin concentration, the oedema depends on changes in functional status and dietary habits and ability of kidney to eliminate the salt and water.

The stimuli leading to this renal salt and water retention in nephrotic syndrome is not clearly understood. It might be expected that hypoalbuminemia would produce a contracted plasma volume with reduced central venous pressure, cardiac output and perfusion of kidneys. These stimuli are known to enhance renal salt retention.

HYPERLIPIDEMIA

Hyperlipidemia is a common accompanyment of the nephrotic syndrome. Low density lipoproteins and cholesterol are elevated most frequently, but as the plasma oncotic pressure falls to very low levels. very low density lipoprotein(VLDL) and triglyceride also increases.

Abnormal serum lipids have been used in the past to justify terming the nephrotic syndrome a metabolic disease. Schreiner described the hyperlipidemia as a secondary manifestation for the following reasons.

- Some patients do not have hyperlipidemia until weeks or months after the development of the other features of the nephrotic syndrome.
- In nephrotic rats, the prevention of proteinurea inhibits the development of hyperlipidemia.

Hyperlipidemia is not found in all the cases of nephrotic syndrome. Kark (1958) described low or normal levels of serum cholesterol in cases of nephrotic syndrome in generalised disease process and indicated it as a poor prognostic feature.

Sarin and Sarin (1960) studied 50 cases of nephrotic syndrome, out of which only 30 cases had hypercholesterolemia above 250 mg%.

Mukerjee (1973) found the hypercholesterolemia in about 43.1% cases of nephrotic syndrome. The normal cholesterol concentration in nephrotic syndrome has been attributed to inadequate intake of diet due to associated nausea, vomiting and diarrhoea of nephrotic syndrome, presence of ezotemia and acute onset of salt retention and oedema due to heart failure.

Shanbhag (1973) studied 116 cases and found that the serum cholesterol was lowest in amyloidosis(177.0 mg%)

followed by membranoproliferative and proliferative glomerulonephritis. Highest serum cholesterol level was noted in end stage or sclerosing group.

Ram Singh et al (1987) studied 650 cases of nephrotic syndrome and found that patients of nephrotic syndrome associated with pulmonary tuberculosis has significantly lower serum cholesterol levels (average 152.4±26.3 mg%) as compared with the cases of nephrotic syndrome associated with other glomerulonephritis (average 419.6±45.7 mg%). Further more he found that the mean serum cholesterol level showed a linear inverse relationship with the duration of pulmonary tuberculosis. 40.9% patients of nephrotic syndrome associated with pulmonary tuberculosis showed hypocholesterolemia whereas none of the patients of the nephrotic syndrome associated with nephritis. Thus the hypocholesterolemia could serve as a pointer of associated pulmonary tuberculosis in nephrotic syndrome.

The exact cause of lipid abnormality in cases of nephrotic syndrome is not clear. Several mechanisms have been proposed so far.

Hypoproteinemia

Human studies have shown a fairly good negative correlation between the level of serum albumin and lipids, which have been reversed following the infusion of the albumin (Baxter, Goodman, Allen, 1961). Schreiner also suggested an inverse but not necessarily straight line

relationship between the serum concentrations of cholesterol and albumin.

Stephen K Newmark et al (1975) found that in nephrotic patients there was significant inverse correlationship between the lipid values and serum albumin but there was no significant inverse relationship between the lipid values and 24 hour urinary protein loss.

It has been suggested that albumin acts as a transport mechanism for the eggress of cholesterol from plasma to bile. A deficiency of serum albumin therefore leaves cholesterol trapped in plasma(Rosenman et al,1956).

According to Valarie Wass et al (1981) the accelerated hepatic lipoprotein production occurs almost certainly as a result of increased protein synthesis by liver in response to abnormal loss of albumin which provides a relatively non specific stimulus for the synthesis of apoproteins and probably other hepatic proteins as well as albumin itself.

Other suggested mechanisms for hypercholesterolemia are changes in the rates of disposal, elimination or interconversion of cholesterol(Baxter et al, 1961). amount of nephrotic tissue and nature of disease 'Hymaen et al, 1958) and thyroid function abnormalities (Peters, JP et al, 1948; Recant et al, 1958; Epstein et al,1926).

Coagulation and Fibrinolytic Abnormalities

Patients with the nephrotic syndrome are apt to develop deep venous thrombosis and pulmonary artery thrombosis especially when given steroid therapy(Pollak et al, 1956; Levine, 1967). The association of renal vein thrombosis and nephrotic syndrome has been known for many years and a recent study reports a very high incidence especially in patients with membranous glomerulonephropathy (Llach, Arieff, Massry, 1975). It is rather difficult to separate out abnormalities due to nephrotic syndrome per se and the effect of therapy particularly steroids. The following abnormalities however, have been described.

1. The plasma fibrinogen level is raised and there is an inverse correlation with serum albumin and positive correlation with the serum cholesterol level. Both synthetic and catabolic rates of fibrinogen are increased in patients with the nephrotic syndrome due to glomerulonephritis (Takeda and Chen, 1967).
2. Coagulation factors V, VII, VIII, X have been reported to be elevated in both untreated nephrotics and those on treatment but not in remission. Mild thrombocytosis and accelerated thromboplastin generation times were also reported (Kendall, Lohmann and Dossetor, 1971).
3. Reduced plasma and urine fibrinolytic activity has been reported in a group of patient in treatment for the nephrotic syndrome(Wardle, Menon, Rastogi, 1970).

AETIOPATHOGENESIS

The nephrotic syndrome is the condition resulted from the excessive glomerular leakage of plasma proteins in the urine. The defect in the charge or size selective barriers of the glomerular capillary wall can arise as a consequence of a wide variety of disease processes including immunologic disorders, toxic injuries, metabolic abnormalities, biochemical defects and vascular disorders. Thus the nephrotic syndrome is not a single disease entity, but the metabolic expression of a wide variety of underlying disease states. It may be the result of :

a. Primary renal disease or idiopathic.

b. Nephrotic syndrome secondary to other diseases.

Idiopathic Diseases

Nephrotic syndrome is said to be idiopathic if it occurs with out a known cause and without any apparent relationship to a systemic disease. They are divided into a variety of histologic classes.

Causes of Nephrotic Syndrome

I. Primary glomerular diseases or idiopathic:

1. Minimal change disease.
2. Mesengial proliferative glomerulonephritis.
3. Membranous glomerulonephritis.
4. Membranoproliferative glomerulonephritis.
5. Focal and segmental glomerulosclerosis.

6. Other uncommon lesions :

- Cresentric glomerulonephritis.
- Focal and segmental proliferative glomerulonephritis.
- Unclassifiable lesions.

II. Secondary to other disorders.

A. Infections

Post streptococcal endocarditis, shunt, nephritis, secondary syphilis, leprosy, hepatitis B, HLTV-III, Infectious mononucleosis, malaria schistosomiasis, filariasis and tuberculosis (Kark, 1958).

B. Drugs

Gold, mercury, pernicillamine, street heroin, probenalid, captopril, Tridione, Mesentoin, Percholate, Antivenum, Antitoxins, and contrast media.

C. Neoplasia

Hodgkins disease, Lymphomas, Leukemia, Carcinomas, Malenoma, Wilm's tumour.

D. Multisystem diseases

SEL, Henoch-schonlein purpura, vasculitis, Good pasture syndrome dermatomyositis, dermatitis, herpetiformis, amyloidosis, sarcoidosis, Sjogren's syndrome, rheumatoid arthritis.

E. Heridofamilial

Diabetes mellitus, alport syndrome, sickle cell disease, Febry's disease, nail patellae syndrome, lipodystrophy, congenital nephrotic syndrome.

F. Misellaneous

Pre-eclamptic toxaemia, thyroiditis, myxoedema, malignant obesity, renovascular hypertension, chronic interstitial nephritis with vesiculouretric reflux, chronic allograft rejection, bee stings.

Minimal Change Disease

Originally recognised by Muller et al (1905) described in detail by Munk and By Velhard and Fahr. This is also known as lipid nephrosis, nil lesion or foot process disease. This is the commonest cause of nephrotic syndrome in children contributing 77% of cases in the international study of kidney disease in children. Although less but still it is found in 25-30% cases of nephrotic syndrome in adult age group.

Typically patients present with overt nephrotic syndrome, normal blood pressure, normal or slightly reduced GFR and a benign urinary sediment, varying degree of microscopic haematuria are found in upto 20% of cases.

Munk (1913) described the term lipoid nephrosis on the basis of tubular changes, included vacuolisation, accumulation of hyline droplets and lipids in the tubular cells and the protenaecous cast in the tubular lumens, but there was no glomerular lesion described.

Tiwari(1987) and Cameron (1974) found following histological changes in the cases of minimal change disease.

	Tiwari (1987)	Cameron (1974)
Glomerular sclerosis	11.8 %	42.8 %
Mesangeal cellularity	9.5 %	46.0 %
Tubular atrophy	17.8 %	51.0 %
Interstitial changes	9.5 %	-
Vascular changes	3.6 %	32.8 %

Electron microscopically there is fusion or effacement of foot processes of glomerular epithelial cells over the surface of the basement membrane. The basement membrane itself is of normal thickness and consists no deposits. There is no cell proliferation, inflammatory infiltrate, fibrosis, or fibrin deposition.

The occasional occurrence of minimal lesion nephrotic syndrome in association with allergic reactions to insect stings, poison ivy, poison oak, or inhaled allergens and usual responsiveness of minimal lesion nephrotic syndrome to corticosteroid or other immunosuppressive therapy suggest a possible immune cause (despite the absence of any glomerular immunoglobulins).

Membranous glomerulonephritis

There is diffuse thickening of glomerular capillary wall without proliferation of the cells. The capillary wall thickening is due mainly to deposition of numerous, irregular electron dense deposits between the basement membrane proper and the epithelial cell cytoplasm.

The epithelial cells overlying the deposits have lost their foot processes and are somewhat swallen. It is the combination of sub-epithelial deposits and altered epithelial cytoplasm that given the appearance of a diffusely thickened basement membrane by light microscopy.

This disorder accounts for about 30-40% of cases of idiopathic nephrotic syndrome, blood pressure, GFR, urinary sediments tends to be normal early in the course. Haematuria or hypertension may occur by they are not constant or necessary features. Renal function usually normal on presentation.

Although most cases of membranous nephropathy are idiopathic, a variety of antigens has been identified been claimed to be pathogenic in those particular patients. These include DNA and C type viral antigens in membranous nephropathy associated with SLE, Hepatitis Bs and Be antigens, thyroglobulins, Tumour antigens;(Malanoma and Cancer of lung and colon), malaria tryponormal antigens, and a renal tubular epithelial cells antigen associated with hemoglobinopathies, renal vein thrombosis and renal cell carcinoma. It is also observed after the exposure of heavy metals (Gold, mercuty), drugs(Penicillamine, Captopril).

Membranoproliferative Glomerulonephritis

This condition is characterised histologically by both thickening of basement membrane and proliferation of cells. Because the proliferation is predominantly in

the masengium, a frequently used synonym is masangio capillary glomerulonephritis. A number of patients with this histologic lesions exhibit persistent hypocomplement-emia and the disease is also known as hypocomplementemic glomerulonephritis.

The glomeruli are large and hyper cellular, the latter due to a prominent increase in mesangial cells. The GBM is thickened often focally, particularly in the peripheral loops. The glomerular capillary wall shows a double contour or tram tack appearance in silver or PAS stains. This is caused by the splitting of basement membrane because of inclusion within it of processes of mesangial cells extending into peripheral capillary loops, so called mesangial interposition.

MPGN is divided into two major subtypes according to ultra structural findings.

Type I

Type I is characterised by presence of sub-endothelial electron dense deposits.

Type II

The lamina dense of glomerular basement membrane (GBM) is transformed into an irregular, electron dense structure due to the deposition of dense material in the GBM proper giving rise to the term dense deposit disease.

MPGN is found in about 7% cases of nephrotic syndrome. It typically causes nephrotic syndrome in

young adults and addlescents, is usually progresses to end stage renal failure. Most series report a slight female preponderance. Nephrotic syndrome is presenting feature in about 40% of patients, Microscopic haematuria with or without RBC casts is a universal finding. Hypertension is found in about 30-50% cases and upto a third have some degree of azotemia when first seen.

As in most other types of glomerulonephritis no etiologic agent is evident. In few instances the MPGN may be found in association with a variety of clinical conditions in which chronic antigenemia may predispose to glomerular disease. Examples of some such conditions include:

- Shunt nephritis - occurs in patients of ventriculo-atrial shunts infected with staph. epidermatitis.
- Some patients with infected endocarditis, chronic active hepatitis and visceral abscesses associated with bacteremia.
- Hepatosplenic form of schistosoma mansoni infection and occasional cases of lupus nephritis or sickle cell nephropathy.

FOCAL AND SEGMENTAL GLOMERULAR SCLEROSIS AND HYLINOSIS

In the course of international study of the effect of corticosteroid therapy in lipoid nephrosis, it was noted that a small proportion of patients responded poorly to steroids. In these patients light microscopic examination of renal biopsies showed that while most

glomeruli were normal, an occasional glomerulus exhibited an area of slcerosis confined to only a segment of the glomerulus. Thus, the lesions were focal in that they involved some glomeruli and segmental in that they involve a segment of the affected glomerulus. Hyline masses were frequently present in the sclerotic areas. Initially the sclerosis involves juxtamedullary glomeruli, subsequently it became more generalised.

Electron microscopy shows, focal basement membrane collapse and denudation of epithelial surfaces. All glomeruli reveal diffuse epithelial foot process effacement Immunofluorescene reveals nodular deposits of IgM and C_3 within aclerotic areas.

Although this is almost certainly a variant of lipoid nephrosis, the entity has now been separated from lipoid nephrosis.

Patients with this lesion have the nephrotic syndrome but differ from usual patients with lipoid nephrosis in the following respects.

1. They have a higher incidence of haematuria and hypertension.
2. They respond poorly to corticosteroid therapy.
3. Many progresses to chronic glomerulitis.
4. Immunofluorescene microscopy shows deposition of IgM and complement in the sclerotic areas of the glomeruli.
5. There is high incidence and recurrence in patients with focal sclerosis, who receives renal transplants.

Mesangial Proliferative Glomerulonephritis

The lesion is characterized by mild to moderate diffuse but distinct increase in the cellularity of the glomerular capillary bed. The peripheral glomerular capillary walls are thin and delicate and extracapillary proliferation is not seen. The precise nature of the proliferating cells is not clearly understood but may represent combinations of proliferating mesangial cells, Endothelial cells and infiltrating mononuclear cells. By immunofluorescence a variety of patterns are observed (IgA, IgM, IgG and C_3)

This lesion accounts for approximately 10% of instances of idiopathic nephrotic syndrome, in adults. Hematurea either gross or microscopic is commonly observed. Loin pain may be present. Renal function may be modestly decreased at the time of diagnosis but is most often normal. The pathogenesis of this lesion, is unknown and almost certainly result of diverse pathogenetic processes. They are unresponsive to corticosteroid therapy and to evolve with time into those of focal and segmental glomerular sclerosis.

TUBERCULOSIS AND NEPHROTIC SYNDROME

The association between pulmonary tuberculosis and nephrotic syndrome is experienced by many workers from very past. But the etiological relationship between the two has not been established yet. Lendonzy and Bernard (1901) described the tuberculosis as a cause of nephrotic syndrome. Bour and Ducomet (1957) described the relation-

ship between lipoid nephrosis and pulmonary tuberculosis.

Mittal et al (1966) studied the renal changes in the pulmonary tuberculosis. They studied 25 cases and found amyloidosis in 2, interstitial nephritis in 1, cloudy swelling in 7 and pyelonephritis in 3 cases. Similar study was carried out by Shah et al (1973). They studied 30 cases and found the membranous glomerulonephritis in 2 cases, amyloidosis in 7 and cloudy swelling in5 cases.

Jain et al (1986) studied the renal changes in 50 cases of pulmonary tuberculosis. out of which 14 cases had the proteinurea of nephrotic range. They biopsied 42 cases, and found membranous glomerulonephritis in 4 cases, proliferative glomerulonephritis in 2 cases, chronic glomerulonephritis in 6 cases, amyloidosis in 2, pyelonephritis in 7 and cloudy swelling in 3 cases.

Most of these changes except for amyloidosis seen to be non specific changes and their aetiologic correlation with pulmonary tuberculosis is debatable.

Of special interest is the present of membranous glomerulonephritis and interstitial glomerulonephritis. It is possible that the initial damage to the kidney parenchyma produced by the tubercle bacilli or its toxins may stimulate release of autoantigens which may perpetuate the process.

Veresnchagin (1958) has incriminated hypersensitivity mediated by tubercle bacilli to be responsible for these changes.

Petrolwala et al (1983) studied 25 cases of nephrotic syndrome out of which 3 cases were associated with pulmonary tuberculosis.

However, many workers of our country and abroad (Sarin and Sarin, 1960; Berman, 1959; Wahi et al, 1962; Prakash, 1965; Johny, KV, 1972; Singh et al, 1987; and Sharma, 1987) found the amyloidosis secondary the tuberculosis as a leading cause of the nephrotic syndrome.

Sarin and Sarin (1960) studied the 50 cases of nephrotic syndrome and found amyloidosis in 33 cases out of which 11 cases were due to pulmonary tuberculosis.

Prakash et al (1965) studied 140 cases of nephrotic syndrome and found the amyloidosis as a second leading cause (32 cases) , out of which 11 cases of amyloidosis were secondary to pulmonary tuberculosis.

Johny KV (1972) biopsied 50 cases of nephrotic syndrome and found amyloidosis in 4 cases of which one was due to miliary tuberculosis and one was due to pulmonary tuberculosis and 2 cases were due to other causes.

Singh et al (1987) studied 650 patients of nephrotic syndrome and found associated tuberculosis in 375 patients. They biopsied 97 cases and found amyloidosis in 65 cases. In these 65 cases tuberculosis was the cause in 60 cases. They found that the mean serum cholesterol levels were significantly low ($p < 0.001$) in those with amyloidosis due to pulmonary tuberculosis.

Sharma et al (1987) studied 250 cases of nephrotic syndrome and found the amyloidosis in 15 cases out of which 9 were secondary due to tuberculosis.

Joel Neugarted et al (1983) described a refampicin induced nephrotic syndrome and acute interstitial nephritis. They admitted a case of pulmonary tuberculosis with normal renal functions and with no urinary protein. They treated the case with R-cin 600 mg and INH 300 mg daily. After 20 days of starting the therapy the blood urea was 50 mg%, serum creatinine 2.1 mg% and 24 hour urinary albumin was 4.1 gm.

INH and Rifampicin were discontinued on 20th day, after 30 days of discontinuation the 24 hour urinary protein excretion was 3.7 gm and after 100 days of discontinuation of therapy. On light microscopy the glomeruli were normal and the interstitium was oedematous and infiltrated by lymphocyte, plasma cells, neutrophils and eosinophils, and electron microscopy showed the focal but extensive effacement of epithelial cell foot processes and the presence of electron dense deposits in mesangial matrix and in sub-endothelial and paramesangeal sites. Co-existing glomerular lesions and acute interstitial nephritis during rifampin therapy have been reported only rarely (Gabow et al, 1976; Bansal et al, 1970; Manasia and Paul, 1975). Gabow et al (1976) suggested that release of tubular antigens as a consequence of rifampicin induced acute interstitial nephritis may give rise to

supper-imposed immune complex glomerulonephritis.

So it is not clear yet that the association of nephrotic syndrome and pulmonary tuberculosis is due to hypersensitivity to tubercle bacilli, or secondary to amyloidosis or secondary to rifampicin therapy.

MATERIAL AND METHODS

MATERIAL AND METHODS

Present study was conducted in the department of Medicine, M.L.B. Medical College, Hospital, Jhansi. In this study 40 cases of nephrotic syndrome in adults admitted in medical wards from June 90 to July, 91 have been included. These 40 cases were taken from consecutive medical units without any selection.

Patients who had 24 hour urinary protein excretion more than 3.5 gm with or without anasarca, hypoalbuminaemia and hypercholesterolaemia were included in the study.

A detailed clinical history was taken including age, sex, occupation, socio-economic status, mode of onset of illness, duration of illness, preceding pharyngeal or skin infections, respiratory infections, diabetes mallitus and pulmonary tuberculosis. The history of oedema, oliguria, hematuria, hypertension, pain in the loin, nausea, vomiting, G.I. bleeding, joint pain, skin rash, allergic disorders, intake of drugs and history any such illness in the family.

Thorough physical examination was conducted including general condition, pulse, B.P., temperature, respiration, pallor, oedema, clubbing, cyanosis, jaundice, lymph nodes and state of hydration. Abdomen was examined for any lump, free fluid in the peritoneal cavity and any evidence of enlarged liver, spleen and kidney. Cardiovacular

other cardiac abnormality. Any disease of nervous system was also ruled out. Examination of respiratory system was done for any clinical evidence of pulmonary tuberculosis, pleural effusion, sarcoidosis, amyloidosis and any other chronic suppurative disease of the lung. The locomotor system was examined for any evidence of arthritis or other features of collagen disorders.

Every patient was investigated for routine investigation like TLC, DLC, Hb, ESR, Complete urinalysis - including albumin, sugar, pus cells, casts, RBCs. and estimation of 24 hour urinary protein excretion was done. Other renal function tests, blood urea, serum creatinine were done in all the cases. Tests for total and differential proteins and serum cholesterol were undertaken. Blood sugar was done to exclude diabetes mellitus in all the cases. General blood picture was also done in all the cases to see any evidence of malarial parasite. X-ray chest PA view and sputum for acid fast facilli were done to see any evidence of pulmonary tuberculosis. Specific tests like LE cell, ANF and rheumatoid factors were done in selected cases.

Percutaneous needle biopsy of kidney was done in all the cases except where the patient was non-cooperative, had severe hypertension, bleeding disorders, or coagulation disorder, single kidney and terminal renal failure. Biopsy was not done in cases of diabetes mellitus due to obvious histopathological changes.

TECHNIQUE OF KIDNEY BIOPSY

Instrument used

Franklin modified Vim-Silverman biopsy needle was used because it gives well cut tissue from the organ (Muhrche et al, 1955).

Preparation of the patient

Every patient prior to kidney biopsy was subjected to bleeding and clotting time to minimise any possibility of bleeding after the procedure. The kidney was located with the help of plain- X-ray abdomen KUB region. Biopsy procedure was thoroughly explained to the patient.

Procedure

After micturition patient was asked to lie prone in the bed. A firm pillow was placed beneath the abdomen to fix the kidney against the back. Biopsy site was chosen in the renal angle at the lower outer poll of the left kidney. Biopsy site is lateral to quadratus lumborum muscle just below th 12th rib.

Biopsy was done with all aseptic precautions. Frequent vitals (pulse rate and blood pressure) were recorded before, during and after the procedure. After infiltration of local anaesthetic agent a lumbar puncture needle of 20 gauze was used for locating the kidney. The patient was asked to take deep breath and to hold it at the height of inspiration, during this breath holding period exploring needle was advanced towards the kidney

at the selected site in the renal angle until a resistance was felt as it penetrates the renal capsule. Patient was then asked to breath out and in repeatedly. When the needle moved back and forth, it confirmed that needle was in the right place.

Now, with the patient holding his or her breath at the height of inspiration, the depth of the kidney from surface was marked on the exploring needle by catching it firmly between thumb and index finger.

Now at the same site, previously measured depth of biopsy needle with stylet was advanced while the patient was asked to take deep breath and hold it when needle was fully advanced to the measured distance, patient was asked to take few breaths and by the movements of the needle its position in right place was confirmed. Patient was then asked to take deep breath and hold it, now stylet was removed and Franklin cutting prongs were inserted to its full depth. Now the outer sheath is pushed down over the cutting prongs which cuts the biopsy tissue from the kidney. The needle and the tissue were quickly pulled out of the back and a firm pressure was applied at the biopsy site with a pad of gauze. The site was dressed with pressure and patient laid in the same position for half an hour. Patient was advised bed rest for 24 hours after biopsy and watched for pulse, B.P. and haematuria.

Tissue thus obtained was fixed in formal saline. The section was stained routinely with haematoxyline and eosine, Mac manus periodic acid Schiff's stain for mucopoly saccharide and gention violet and Congo red stains for amyloid in selected cases by standard techniques.

The data obtained by clinical examination of the patients and the histopathological findings were statistically analysed.

OBSERVATIONS

OBSERVATIONS

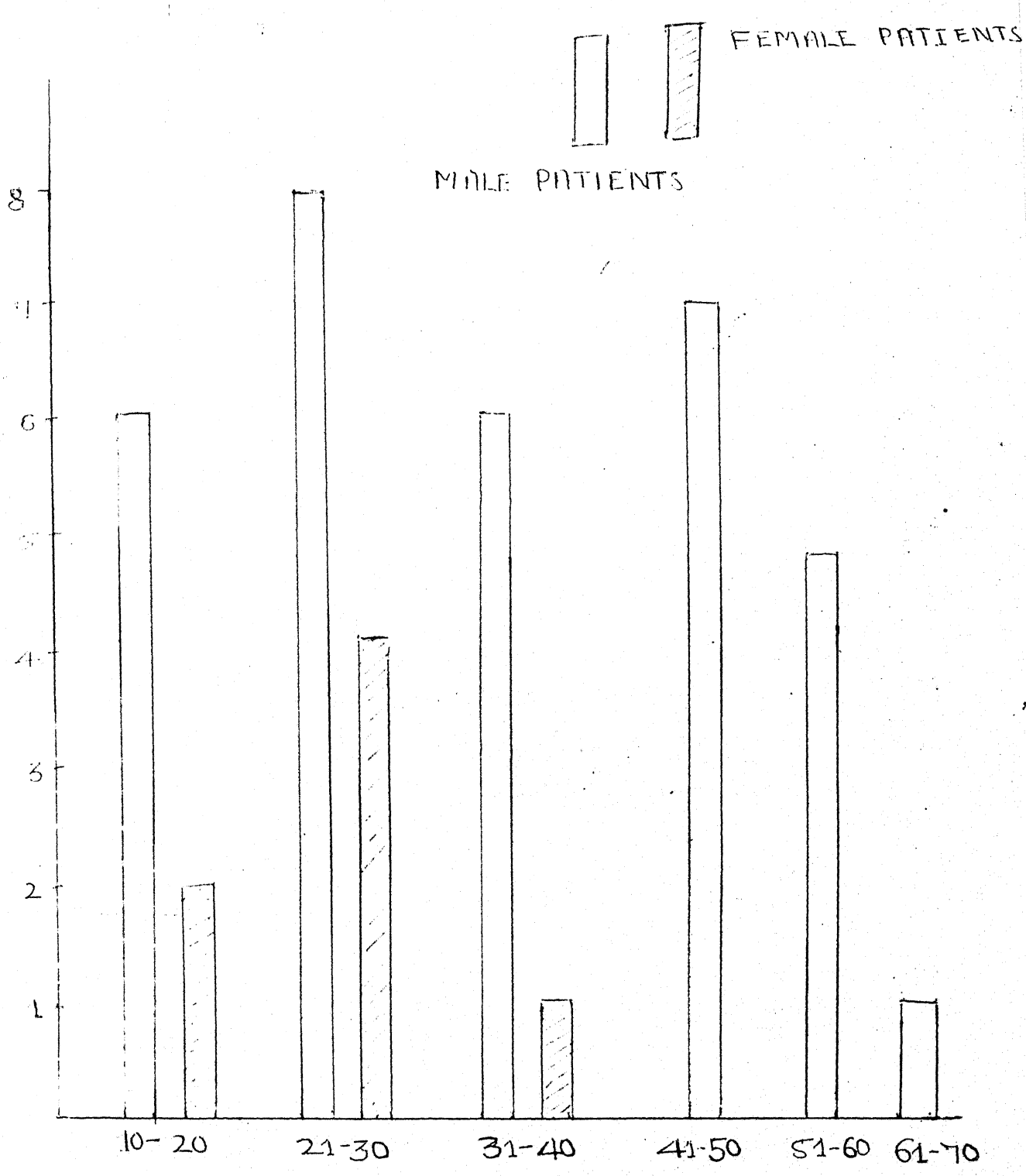
In this study 40 cases of nephrotic syndrome were included. Age and sex distribution of these 40 cases is shown in table

TABLE 1 : Age and sex distribution of the cases.

Age group (years)	Total		Male		Female	
	No.	%	No.	%	No.	%
10 - 20	8	20.0	6	15.0	2	5.0
21 - 30	12	30.0	8	20.0	4	10.0
31 - 40	7	17.5	6	15.0	1	2.5
41 - 50	7	17.5	7	17.5	-	-
51 - 60	5	12.5	5	12.5	-	-
61 - 70	1	2.5	1	2.5	-	-
TOTAL	40	100.0	1	82.5	7	17.5

The age of the cases ranged from 14 to 65 years. The mean age for the males was 36.36 years and for females it was 25.42 years. The average mean age for both the sexes was 34.45 years. Out of 40 cases 33 were males and remaining 7 were females. The male to female ratio was 4.7 : 1.

The maximum number (50%) of cases were in the 2nd and 3rd decades of life.



BAR DIAGRAM SHOWING AGE AND SEX DISTRIBUTI

IN 40 PATIENTS OF NEPHROTIC SYNDROME

TABLE 2 : Showing the duration of illness at the time of the study.

Duration (Months)	No.of cases	Percentage	Mean
∠ 1	12	30.0	
1 - 2	6	15.0	
2 - 4	8	20.0	4±2.9
4 - 12	13	32.5	
12 - 24	1	2.5	
TOTAL	40	100.0	

Table 2 shows the duration of illness in 40 cases which ranged from 12 days to 24 months. 12(30%) cases were having duration of illness of less than one month. All cases except 1 were within 1 year of duration. The mean duration of illness was 4±2.9 months.

Table 3 shows the frequency of symptoms with which the disease started. 6(15%) cases had swelling all over the body without any other features. 5(12.5%) cases had associated decreased appetite, 4(10%) patients had associated oliguria and 3(7.5%) cases had associated symptoms of oliguria.andSwelling over feet without any other symptoms was found in 2(5%) cases only. Cough and expectoration was present in 18(45%) cases, out of these 18 cases only 3(7.5%) cases had breathlessness and 15 (37.5%) cases had decreased appetite. Oliguria was present in only 2(5%) cases at the time when they

TABLE 3 : Showing different symptoms at the time of onset of the disease.

Symptoms	No.of cases	Percentage
1. Swelling over feet	2	5.0
2. Swelling over the body	6	15.0
3. Swelling all over the body with decreased appetite	5	12.5
4. Swelling all over the body with oliguria	4	10.0
5. Swelling over feet with symptoms suggestive of diabetes mellitus	3	7.5
6. Oliguria	2	5.0
7. Cough with expectoration with decreased appetite	15	37.5
8. Cough with expectoration wi and breathlessness.	3	7.5
TOTAL	40	100.0

Table 4 shows that oedema was present in all the cases and ascites was found to be present in 16(40%) cases and pleural effusion was present in only 4(10%) cases. 10(25%) cases had hypotension while 7(17.5%) cases had hypertension. Productive cough was present in 18(45%) cases, 13 cases had decreased appetite, out of which 8 (20%) cases had nausea and vomiting. Only 2(5%) cases had history of fever. Breathlessness was present in 16(40%) cases and oliguria was present in 6(15%) cases. On 1(2.5%) cases complainted of haematuria.

TABLE 4 : Showing the frequency of clinical features present during whole course of the disease.

Sl. No.	Clinical feature	No.of cases	Percentage
1.	Oedema	40	100.00
2.	Ascites	16	40.00
3.	Pleural effusion	4	10.00
4.	Hypotension	10	25.00
5.	Hypertension	7	17.50
6.	Cough	18	45.00
7.	Expectoration	18	45.00
8.	Nausea and vomiting	8	20.00
9.	Fever	2	5.00
10.	Decreased appetite	5	12.50
11.	Breathlessness	16	40.00
12.	Haematuria	1	2.50
13.	Oliguria	6	15.00

Table 5 shows that total leucocyte count was normal in 30(75%) cases. It was increased in 6(15%) cases, while it was slightly below the normal in 4(10%) cases. 20(50%) patients were having polymorphonuclear leucocytosis. Almost all these 39(97.5%) cases were having raised erythrocyte sedimentation rate. Only one patient had normal ESR. Majority of these (90%) had anemia.

TABLE 6 : Showing urinary findings in 40 cases.

Examinations	No.of cases	Percentage
Urinary output/24 hours		
⟨400 ml	2	5.00
⟩400 ml	38	95.00
Microscopic examination		
Pus cells	10	25.00
Epithelial cells	12	30.00
Casts	1	5.00
Phosphate crystals	5	12.50
R.B.Cs.	1	2.50
Protein excretion (gm/24 hours)		
3.5 - 5	10	25.00
5 - 10	26	65.00
⟩ 10	4	10.00

Table 7 shows that total serum proteins were decreased below 5.5 gm/dl in 22(55%) cases but it was normal in around 45% cases. But albumin fraction alone was decreased in more cases. It was below 3.5 gm in 30(75%) cases and normal in around 25% cases. Quite a significant number i.e. 25(62.5%) cases had increased level of serum cholesterol but 15(37.5%) cases had normal cholesterol levels.

Only 4(10%) patients had Diabetes Mellitus whose fasting and post prandial values were increased above 120 and 200 mg/dl respectively.

TABLE 5 : Showing blood count haemoglobin and ESR in study cases.

Blood values		No.of cases	Percentage
T.L.C.	: Normal	30	75.00
	7 11000	6	15.00
	∠4000	4	10.00
Polymorph	: Normal	15	37.50
	7 65%	20	50.00
	∠30%	5	12.50
Lymphocyte	: Normal	30	75.00
	7 45%	4	10.00
	∠ 30%	6	15.00
E.S.R.	: Normal	39	97.50
	7 20	1	2.50
Haemoglobin	: 7 11.5 gm%	4	10.00
	∠ 11.5 gm%	36	90.00

Table 6 shows that 2(5%) cases were having oliguria. Microscopic examination of urine shows pus cells in 10(25%) cases. Epithelial cells in 12(30%) cases and phosphate crystals in 5(12.5%) cases, but casts and R.B.Cs. were present in 1(2.5%) case. 10(25%) cases had less than 5 gm/24 hour urinary protein excretion and 4(10%) cases had more than 10 gm/24 hours protein excretion but majority of the patients (65%) had moderate amount (5-10 gm) protein excretion in 24 hours.

TABLE 7 : Showing various biochemical findings in 40 cases of nephrotic syndrome.

Biochemical findings	No.of cases	Percentage
Total serum proteins (gm/dl)		
∠ 5.5	22	55.00
7 5.5	18	45.00
Serum albumin (gm/dl)		
∠ 3.5	30	75.00
7 3.5	10	25.00
Serum cholesterol (mg/dl)		
7250	25	62.50
∠ 250	15	37.50
Blood sugar (mg/dl)		
F - 7 120	4	10.00
PP - 7 200	4	10.00
Blood urea (mg/dl)		
∠ 40	16	40.00
40-100	21	52.50
7 100	3	7.50
Serum creatinine (mg/dl)		
∠ 1.5	16	40.00
7 1.5	24	60.00

Blood urea was raised in 24(60%) cases. Out of these 24 cases, it was raised beyond 100 mg/dl in 3 cases. It was found within normal limits in 16(40%) cases. 24 (60%) cases had raised levels of serum creatinine.

RELATIONSHIP BETWEEN SERUM ALBUMIN AND OEDEMA

TABLE 8 : Relationship between serum albumin and oedema

Serum albumin (gm%)	Pedal oedema		Gen. Oedema		Total	
	No.	%	No.	%	No.	%
1.0 - 1.5	-	-	-	-	-	-
1.6 - 2.5	2	5.0	4	10.0	6	15.0
2.6 - 3.5	2	5.0	22	55.0	24	60.0
73.5	1	2.5	9	22.5	10	25.0
TOTAL	5	12.5	35	87.5	40	100.0

Table 8 shows that pedal oedema was present in 5(12.5%) cases and generalised oedema in 35(87.5%) cases. The serum albumin was normal in 10(25%) cases. Out of which 1 case had pedal oedema and 9 had general oedema. The serum albumin was markedly decreased (1.6-2.5 gm%) in 6(15%) cases, 2(5%) of them had pedal oedema and 4(10%) cases had general oedema.

Serum albumin level ranged between 2.6-3.5 gm% in maximum number(24, 60%) of cases. Out of these 2(5%) had pedal oedema and 22(55%) had general oedema. None of the case had serum albumin less than 1.5 gm%.

Table 9 shows that out of 40 cases studies, only 31 cases could be biopsied, rest 9 cases could not be biopsied as 4 cases had diabetes mellitus, 1 patient was in terminal renal failure, 3 cases were non co-operative and 1 patient was in poor general condition with severe hypotension.

TABLE 9 : Study of renal biopsy in 40 cases of nephrotic syndrome.

Biopsy	No.of cases	Percentage
A. Biopsy done	31	77.50
B. Biopsy not done due to		
- Diabetes	4	10.00
- Non-cooperation by the patients	3	7.50
- Terminal renal failure	1	2.50
- Poor general condition	1	2.50
TOTAL	40	100.00

TABLE 10 : Histological diagnosis of 31 cases of nephrotic syndrome.

Histological type	No.of cases	Percentage
1. Membranous glomerulonephritis	16	51.6
2. Membrano-proliferative glomerulonephritis	8	25.8
3. Mesangial proliferative glomerulonephritis	1	3.2
4. Amyloidosis	4	12.9
5. Not clear due to inadequate biopsy sample	2	6.5

Table 10 shows histopathological lesions in 31 patients who were biopsied. Membranous glomerulonephritis was a leading cause of nephrotic syndrome as it was present in 16(51.6%) cases following by membrano-

TABLE 11 : Major clinical and biochemical findings in each histological group of nephrotic syndrome.

Histological group	Mean duration of oedema (months)	Mean proteinuria (gm/24 hrs)	Mean serum albumin (gm%)	Mean blood Urea (mg/dl)	Mean serum cholesterol (mg/dl)	Mean serum creatinine (mg%)
Membranous glomerulonephritis	3.6	6.4	3.0	43	290	1.6
Membranoproliferative glomerulonephritis	4.4	6.2	2.9	56	300	2.0
Mesangial proliferative glomerulonephritis	6.0	8.2	1.8	120	406	2.8
Amyloidosis	4.6	8.3	2.0	38	230	1.8
Diabetes mellitus	2.4	4.7	2.8	36	363	1.3
Others	6.0	6.0	2.6	42	190	1.4
Mean	4.5	6.6	2.5	55	296	1.8

proliferative glomerulonephritis which was present in 8(25.8%) cases. Amyloidosis was present in 4(12.9%) cases. Mesangial proliferative glomerulonephritis was present in only 1 case and in 2 cases histopathological identification could not be made because of inadequate kidney tissue.

Table 11 shows major clinical and biochemical findings in various histological groups. Mean duration of oedema was 2.4 months in cases of diabetes and 6 months in cases of mesangial proliferative glomerulonephritis. Mean urinary protein excretion was 6.6 gm/24 hour. Mean protein excretion was maximum 8.2 gm/24 hours in mesangial proliferative glomerulonephritis and it was lowest (4.7 gm/24 hours) in diabetic nephropathy. Average serum albumin was 2.5 gm%. It was lowest in mesangial proliferative glomerulonephritis and highest in membranous glomerulonephritis. Mean serum cholesterol was 296 mg%. It was highest (406 mg%) in mesangial proliferative glomerulonephritis while lowest (230 mg%) in cases of amyloidosis and even lower in those 2 cases where renal lesion could not be determined but both of these cases were having pulmonary tuberculosis.

Average blood urea was 55 mg%. It was highest 120 mg% in cases of mesangial proliferative glomerulonephritis and lowest (36 mg%) in diabetes mellitus. Mean serum creatinine was 1.8 in study cases. Serum creatinine was highest(2.8 mg%) in mesangial proliferative glomerulonephritis and lowest (1.3 mg%) in diabetes mellitus cases.

TABLE 12 : Showing the relation of blood pressure and histological types of nephrotic syndrome.

Histological type	No.of cases	Normal B.P. No.(%)	Hypertension BP 790 mm Hg diastolic No. (%)	Hypotension BP ⟨90 mm Hg systolic No.(%)
Membranous glomerulonephritis	16	8(50)	2(12.5)	6(37.5)
Membranoproliferative glomerulonephritis	8	5(62.5)	2(25)	1(12.5)
Mesangial proliferative glomerulonephritis	1	-	1(100)	-
Amyloidosis	4	3(75)	-	1(25)
Diabetes mellitus	4	2(50)	2(50)	-
Others	2	2(100)	-	-
TOTAL	35	20(57.2)	7(20)	8(22.8)

Table 12 shows the relation of B.P. and histological type of nephrotic syndrome in 35 cases. 57.2% cases had normal blood pressure, 20% had hypertension and 22.8% cases had hypotension (⟨90 mm Hg systolic).

In membranous glomerulonephritis cases out of 16, 8(50%) cases had normal blood pressure, 2(12.5%) cases had hypertension and 6(37.5%) cases had hypotension. In 8 cases of membranoproliferative glomerulonephritis, 5 (62.6%) cases

TABLE 13 : Relations of renal functions and various histopathological types of nephrotic syndrome.

Histopathological group	No.of cases	Raised blood urea (7 40 mg%) No. (%)	Serum creatinine 7 1.5 No. (%)	Creatinine clearance		
				Mild 75-50 No. (%)	Moderate 50-20 No. (%)	Severe 7 20 No. (%)
Membranous glomerulonephritis	16	8(50)	9(56.25)	6(37.5)	3(18.75)	-
Membranoproliferative glomerulonephritis	8	6(75)	8(100)	4(50)	3(37.50)	1(12.50)
Mesangial proliferative glomerulonephritis	1	1(100)	1(100)	-	1(100)	-
Amyloidosis	4	3(75)	2(50)	1(25)	-	1(25)
Diabetes mellitus	4	3(75)	3(75)	2(50)	-	1(25)
Others	2	1(50)	1(50)	1(50)	-	-
TOTAL	35	22(62.85)	24(68.57)	14(40)	9(25.7)	1(2.8)

had normal blood pressure and 2(25%) cases had hypertension, only 1 case (12.5%) had hypotension.

Only 1 case of mesangial proliferative glomerulonephritis had hypertension. In 4 cases of amyloidosis only 1(25%) case had hypotension and rest 3 (75%) cases had normal blood pressure. In 4 diabetic patients, 2(50%) of them were hypertensive.

Table 13 shows renal function in 35 histologicall proved cases. In membranous glomerulonephritis blood urea was raised in 50% cases and serum creatinine in 56.25% cases having mild reduction of creatinine clearance in 37.5% cases and moderate reduction in 18.75% cases.

Out of 8 cases of membranoproliferative glomerulonephritis, 6(75%) cases had raised blood urea and serum creatinine. Out of these 6 cases, 50% had mild reduction in creatinine clearance, 37.5% had moderate reduction in creatinine clearance and severe reduction in creatinine clearance ($\angle$20 ml/min) was found only in 1(12.5%) case.

In 1 case of mesangial proliferative glomerulonephritis serum creatinine and blood urea was raised and creatinine clearance was moderately decreased.

In amyloidosis mild to moderate reduction in creatinine clearance was present in 50% cases. However, in diabetic nephropathy, 2(50%) cases had mild reduction in creatinine clearance while moderate reduction in creatinine clearance was present in 1(25%) case only.

TABLE 14 : Showing the presence of associated diseases in cases of nephrotic syndrome.

Associated disease	No.of cases	Percentage
Tuberculosis	21	52.50
Diabetes mellitus	4	10.00
Chronic obstructive airway disease	2	5.00
Bronchiectasis	2	5.00
Without any illness	11	27.50
TOTAL	40	100.00

Table 14 shows that patients of nephrotic syndrome were found to be associated with other diseases as well. They included 21 (52.50%) cases of tuberculosis, 4(10%) cases of diabetes mellitus, 2(5%) cases of COAD and 2(5%) cases of bronchiectasis and rest 11(27.50%) cases were not associated by any other illness.

Thus from the above table it is evident that pulmonary tuberculosis was frequently associated with nephrotic syndrome. cases.

Table 15 shows relation of duration of pulmonary tuberculosis with nephrotic syndrome. It is recognised by its clinical symptoms, namely cough and expectoration. The duration of pulmonary tuberculosis does not show any relation to development of nephrotic syndrome. In addition to these 18cases, 1 case of diabetes was also having pulmonary tuberculosis and there were 2 cases of Pott's spine thus total number of cases of tuberculosis were 21.

TABLE 15 : Showing duration between symptoms of pulmonary tuberculosis and onset of nephrotic syndrome.

Duration (months)	No.of cases	Percentage
0 - 2	2	11.1
2 - 4	4	22.2
4 - 6	4	22.2
6 - 8	2	11.1
8 - 10	1	5.6
10 - 12	2	11.1
12 - 18	1	5.6
7 18	2	11.1
Total	18	100.0

TABLE 16 : Relation of antitubercular treatment with the development of nephrotic syndrome.

Nephrotic syndrome cases with pulmonary tuberculosis	No.of cases	Percentage
Without antitubercular treatment before admission in the hospital	11	52.30
On antitubercular treatment before development of N.S.	10	47.70
TOTAL	21	100.00

Table 16 shows that out of 21 cases of tuberculosis with nephrotic syndrome, 11 (52.3%) were not taking any antitubercular treatment while 10(47.7%) cases were on antitubercular treatment. So there seems to be no relationship between development of nephrotic syndrome with or without antigercular treatment.

TABLE 17 : Relationship between histological types of nephrotic syndrome and pulmonary tuberculosis.

Histological types	No.of cases	Pulmonary tuberculosis	
		No.	%
Membranous glomerulonephritis	16	11	68.75
Membranoproliferative glomerulonephritis	8	2	25.00
Mesangial proliferative glomerulonephritis	1	-	-
Amyloidosis	4	4	100.00
Diabetes mellitus	4	1	25.00
Others	2	1	50.00
TOTAL	35	19	

Table 17 shows that all the cases of amyloidosis had tuberculosis. 11(68.75%) cases out of 16 cases of membranous glomerulonephritis had tuberculosis. 25% of the membranoproliferative glomerulonephritis and diabetes mellitus cases had tuberculosis. Mesangial proliferative glomerulonephritis cases had no tuberculosis. Besides these 19 cases of tuberculosis remaining 2 cases of tuberculosis could not be biopsied. So membranous

glomerulonephritis and amyloidosis were most frequent histological lesion in cases of nephrotic syndrome with pulmonary tuberculosis.

TABLE 18 : Frequency of amyloidosis in cases of nephrotic syndrome with pulmonary tuberculosis.

Nephrotic syndrome with pulmonary tuberculosis	No.of cases	Percentage
With amyloidosis	4	21.00
Without amyloidosis	15	79.00
TOTAL	19	100.00

Thus it is clear from the table 18 that only 21% cases of tuberculosis had nephrotic syndrome because of renal amyloidosis, but remaining 79% cases of pulmonary tuberculosis had nephrotic syndrome because of non amyloidosis lesions like membranous glomerulonephritis, Membranoproliferative glomerulonephritis, diabetes mellitus and others.

DISCUSSION

DISCUSSION

Nephrotic syndrome is a disease which can occur in any age group from infancy to extremes of age. In the present study the youngest case was of 14 years and olest was of 65 years of age.

Nephrotic syndrome affects males more often than females. The male to female ratio was 4.7 : 1 and almost similar (4:1) ratio has been reported by Sarin and Sarin (1960). While Prakash et al (1965), Mukerjee et al (1973) and Sharma et al (1987) reported that this ratio was 2.3:1, 2.2:1 and 2 : 1 respectively.

In the present study maximum number of cases occurred in 3rd decade of life. Mukerjee et al (1973) also found the maximum number of cases in 3rd decade of life. Sharma et al (1987) and Sarin and Sarin (1960), Shanbhag (1973) also reported maximum number of cases in 2nd and 3rd decade of life.

The commonest presenting feature was oedema in the present study. It was present in 20(50%) cases at the time of onset of the disease but later on with the progression of disease all the 40(100%) cases had oedema. The oedema was reported in all the cases by Mukerjee et al (1973), Shanbhag et al (1973) and Sharma et al (1987). Like present study, Sarin and Sarin (1960) also found oedema in 56% of the cases initially but later on all of them developed oedema. But oedema was absent in 24% cases of nephrotic syndrome studied by Berman et al (1958).

Hypoproteinaemia, more specifically hypoalbuminaemia was said to have relationship between occurrence and severity of oedema and concentration of serum albumin. Squire et al (1957) found that anasarca and paedal oedema were present when albumin level in the serum was below 1.6 and 1.8 gm% respectively but this view does not holds true any more, as Berman (1958) reported general anasarca with serum albumin level more than 2.5 gm%. Shreiner (1963) reported absence of oedema even serum albumin concentration was below 2.0 gm%. In the present study serum albumin less than 3.5 gm% was present in 30(75%) cases while 10(25%) cases had normal serum albumin level.

Cases in which serum albumin levels was less than 2.5 gm% were only 6 in number (15%). Out of which only 4 had general oedema and 2 had pedal oedema. On the contrary patients who had normal serum albumin level(more than 3.5 gm%) were 10(25%) in number. Out of them 9 (22.5%) cases had general oedema and 1 had paedal oedema Thus these findings suggests that hypoalbuminaemia is not the only cause responsible for oedema but threre are many other factors which decides the development of oedema, these includes dietary habits (Schreiner, 1963), Changes in functional status and ability of kidneys to eliminate salt and water. In nephrotic syndrome sodium retention occurs possibly due to reduction in glomerular filteration rate or due to increased secretion of aldosterone

resulting from hypovolumia or increased formation of renin and angiotensin.

The duration of oedema ranged from 12 days to 2 years. Except one case, the duration of illness was less than one year in all cases. Sarin and Sarin (1960) also found the duration of symptoms mainly oedema less than 1 year in 92% of cases.

Various other clinical features which were present during the course of the illness were as follows. pleural effusion was present in 4(10%) cases, while other workers, Prakash et al (1965) reported in 18% cases and Sharma et al (1987) reported in 11% cases. Ascites was found in 16(40%) cases. This corresponds with the observation of Prakash et al (1965) - 43%, and Sharma et al(1987)- 34%. However, Mukerjee et al (1973) reported it to be in 94% of the cases.

Hypertension was found in 7(17.5%) cases in the present study while Prakash et al (1985) recorded it in 23% cases. However, Mukerjee reported hypertension in 44% cases.

An uncommon observation in the present study was occurrence of hypotension. The systolic blood pressure $\angle$90 mm Hg was found in 10(25%) cases. 8 cases of them had tuberculosis and 2 had no other associated illness. Histologically 6 of them were having membranous glomerulonephritis. One had membranoproliferative glomerulonephritis.

and 1 had amyloidosis. In rest wo cases histopathological features were not clear.

Shanbhag et al (1973) in their study showed 3 cases with hypotension out of 116 cases and two of them were having amyloidosis. This difference in histology showed absence of any relationship between hypotension and amyloidosis as Shanbhag illustrated.

In the present study most of the cases were having associated pulmonary tuberculosis and the addison's disease might be a cause of hypotension in these cases. Administration of diuretics and reduced blood volume may also have contributed to the developments of hypotension. However, no other worker from India and abroad has reported hypotension in their cases of nephrotic syndrome.

Hypoproteinaemia was present in 55% cases of present study. But Mukerjee et al (1973), Shanbhag (1973) and Prakash et al (1965) reported hypoproteinaemia in 74%, 73% and 63% respectively but due to associated changes and rise in globulin fraction total serum proteins is not a reliable indicator of urinary protein.

In the present study hypoalbuminaemia was found to be present in 75% cases. Estimation of serum albumin was more significant than estimation of total serum protein as urinary lose of proteins occur mainly in the form of albumin.

Hypercholesterolaemia ($\bar{7}$250 mg%) was seen only in 62.5% cases in present study. But Prakash et al (1965) found hypercholesterolaemia in 73%. This difference may be explained on the basis of inclusion of more cases having pulmonary tuberculosis which is associated with lower plasma cholesterol levels (Singh and Singh, 1987). But Shanbhag reported hypercholesterolaemia in 63% cases which is quite compatible with the present study.

Blood urea was found to be raised ($\bar{7}$40 mg%) in 60% cases but most of the cases (52.5%) were having blood urea level less than 100 mg/dl. Other workers from India Prakash et al (1965), Mukerjee et al (1973), and Shanbhag et al (1973) reported it in lesser number of patients i.e. 20%, 34%, and 27% respectively but remarkable difference may be explained on the basis of later presentation of our cases due to low socio-economic status and poor educational background in Bundelkhand region.

Aetiological factors in different studies in India and aborad are quite variable, which may be due to multiple factors. One of them could be use of different classification of nephrotic syndrome by different workers in different studies . Other factors may be regional factors depending upon social environment factors(Hayslett et al, 1973; Kar, 1958; Sarin and Sarin, 1960; Prakash et al, 1965; Vaishwara and Gulari, 1966; Mukerjee et al, 1973; Shanbhag et al, 1973 and Sharma et al, 1987).

COMPARATIVE INCIDENCE OF HISTOLOGICAL LESIONS IN DIFFERENT STUDIES OF NEPHROTIC SYNDROME.

Authors	Total No.of cases	MGN	MPGN	PGN	MLGN	Other
Pearl et al,1963	34	11	8	7	9	-
Schreiner, 1963	111	41	-	36	-	34
Cameron, 1966	62	29	-	14	5	14
Mukerjee et al,1973	116	39	6	18	3	50
Sharma et al,1987	250	14	44	35	64	63
Present study,1991	31	16	8	1	-	6

In our study of 31 biopsy cases, membranous glomerulonephritis was the commonest lesion found in 51.6% cases of nephrotic syndrome. Similarly Schreiner (1971) found 47% cases of membranous glomerulonephritis in a collaborative study of adult nephrotic syndrome. From our country Prakash et al, Mukerjee et al and Shanbhag et al found 48%, 33% and 47% cases of membranous glomerulonephriti respectively.

Membranoproliferative glomerulonephritis constituted 25% cases in our study which is in agreement with Pearl et al (1963) (23.5%) but others reported it in lesser numbers e.g. Mukerjee et al (1973) - 5.2%, Shanbhag et al (1973) - 8.9%, Sharma et al (1987) reported it as 17.6% cases.

Proliferative glomerulonephritis was found in 3.2% cases in our study which is reported as 8% by Sharma et al (1987).

The minimal lesion glomerulonephritis was found absent in our study. Schreiner (1963) also found no case of MLGN, but on the contrary Sharma et al (1987) found the MLGN as commonest cause of nephrotic syndrom.

In our study Diabetes Mellitus and amyloidosis were found to be the secondary causes of nephrotic syndrome. The amyloidosis was present in 4(12.9%) cases out of 31 biopsy cases and it seems reasonable to say that it was because of pulmonary tuberculosis which was present in all the four cases. Sarin and Sarin (1960) found the amyloidosis in 66% cases of nephrotic syndrome. Prakash et al found renal amyloidosis in 22.8% cases but Sharma et al (1987) found it only in 6% cases and Mukerjee et al (1973) in none.

In the present study of 40 cases only 4 cases (10%) were found to be diabetic. These cases of diabetes mellitus were not biopsied because they were assumed to be the cases of diabetic nephropathy. Berman (1958) reported 7.3%. Sarin and Sarin (1960) reported as 4%, and Wahi (1962) - 9.4%. However, Mukerjee et al (1973), Sharma et al (1987) found diabetic nephropathy in 17.2% and 18.8% cases respectively.

There seems to be some association of nephrotic syndrome with tuberculosis but causal relationship was not established but in present study 21 out of 40 cases of nephrotic syndrome had tuberculosis which is 52.5% which is statistically highly significant finding.

In most of the earlier studies of nephrotic syndrome Sarin and Sarin (1960), Wahi et al (1962), Prakash et al (1965), Johney et al (1972) and Sharma et al (1987) in which tuberculosis was present. It was concluded that tuberculosis had led to the development of amyloidosis causing nephrotic syndrome.

However, Shah (1975) studied and biopsied 30 cases of pulmonary tuberculosis and found amyloidosis in 7 cases only and membranous glomerulonephritis in 2 cases. showing that the membranous glomerulonephritis may also be cause of proteinuria in the cases of pulmonary tuberculosis associated with nephrotic syndrome.

Similarly Singh et al (1987) studied 150 cases of nephrotic syndrome out of which 97% cases were associated with tuberculosis and 60 of them were having amyloidosis. Remaining 37 cases of nephrotic syndrome associated with pulmonary tuberculosis in which non amyloid lesions were responsible for the development of nephrotic syndrome.

Thus in cases of tuberculosis it is very likely that proteinurea was not only due to development of amyloidosis but due to membranous glomerulonephritis or some other kidney pathology.

Jain et al (1986) biopsied 42 cases of pulmonary tuberculosis and found abnormal histology in 23 cases, of which 14 were in nephrotic range. These abnormal histological diagnosis included amyloidosis in 2 cases, membranous glomerulonephritis in 4 cases, proliferative glomerulonephritis in 2, chronic pyelonephritis in 7 and cloudy swelling in 3 cases.

In present study amongst the cases of nephrotic syndrome with pulmonary tuberculosis, amyloidosis was present in 4 cases. 11 cases had membranous glomerulonephritis, 2 cases were having membranoproliferative glomerulonephritis. Three cases were not biopsied due to presence of diabetes mellitus. Most of these changes in tuberculosis are non-specific except amyloidosis and their aetiological correlation is debatable.

Keeping all these things in mind membranous glomerulonephritis seems to be of special interest found in present study. (Shah et al (1975) and Jain et al(1986). It seems likely that damage to kidney parenchyma is produced by tubercular bacilli directly or indirectly to stimulate the release of autoantigens which perpetuate the process of further kidney damage.

In this study of 21 cases of pulmonary tuberculosis with nephrotic syndrome were found. Duration between pulmonary tuberculosis and nephrotic syndrome ranged from 1 month to more than 18 months and all the

cases were scattered between these two extremes. Thus, it shows that chances of development of nephrotic syndrome are not related with the duration of pulmonary tuberculosis.

Development of nephrotic syndrome was unrelated to antitubercular treatment in our study as shown by the fact that 52.3% cases were without antitubercular treatment and 47.7% cases were on antitubercular treatment which shows almost equal incidence of nephrotic syndrome in both the groups. It rules out any possible contribution of antitubercular drugs in the development of nephrotic syndrome.

C O N C L U S I O N

CONCLUSION

From the present study conducted on 40 patients of nephrotic syndrome following salient features were concluded.

1. Maximum number of cases of nephrotic syndrome belonged to 3rd decade of life.
2. Males are affected more commonly than females and males to female ratio was 4.7 : 1.
3. Chief clinical features in the cases of nephrotic syndrome were found as general anasarca, paedla, oedema, cough with breathelessness, ascitis, pleural effusion.
4. Hypotension was a peculiar feature of nephrotic syndrome found in 8 cases and were associated with tuberculosis and deteriorated faster.
5. Hypoalbuminaemia occurred in 75% of the cases but linear relationship between hyplalbuminaemia and oedema is not present.
6. Serum cholesterol was increased in 62.5% cases.
7. Diabetes mellitus and amyloidosis were found to be the secondary causes of nephrotic syndrome.
8. Membranous glomerulonephritis and membranoproliferative glomerulonephritis were found to be the commonest histological lesions in this study.

9. 52.5% cases were found to be associated with tuberculosis and histologically had membranous glomerulonephritis as most frequently occurring lesion.

10. Amyloidosis was secondary to pulmonary tuberculosis in all 4 cases of this study.

11. There was no effect of duration of pulmonary tuberculosis and antitubercular treatment on the development of proteinurea.

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